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(54) **Complexes and chelates of azithromycin as antiulcer drugs.**

(57) The invention relates to the use of complexes and chelates resp., of antibiotics, especially azithromycin, with bivalent and/or trivalent metals in the obtaining of antiulcer drugs, to new complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals and to processes for the obtaining thereof.

The present invention relates to the use of complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals in the obtaining of antiulcer drugs, to new complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals and to processes for the obtaining thereof.

It has been known that some organic compounds form metal complexes and chelates, thereby changing their physical-chemical properties (solubility, stability, melting point etc.) and the pharmacokinetics as well as the pharmacodynamics in biologically active compounds.

There was described (BE patent 892,357) the formation of Co^{+2} complexes of macrolide antibiotics, especially of erythromycin, the starting substance for obtaining N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (non-proprietary name azithromycin; proprietary name Sumamed® (PLIVA, Zagreb, Yugoslavia), whereas J. Pharm. Pharmac. 18, (1966) 727 asserts that with other divalent metal ions (Cu^{+2} , Ca^{+2} , Mg^{+2} , Ni^{+2} and Zn^{+2}) no complexes are formed. On the contrary, we have found that azithromycin forms complexes with bivalent metals yielding products of a high antibiotic activity (HU patent 198,507).

It has been known that *inter alia* Al-Mg gel is applied as antacid in the treatment of duodenal or gastric ulcer giving relief to the gastric mucosa and keeping the pH of the gastric juice between 4.5 and 5.5. For the same purpose also some antibiotics have been used in order to eradicate the microorganisms *Helicobacter pylori* and *Campylobacter jejuni* which are allegedly one of the factors causing the development and the relapse of duodenal or gastric ulcers. Since it has been presumed that *Helicobacter pylori* inhabits the mucous region of the gastric membrane - whereby the often unsuccessful eradication and the resulting recurrences have been explained - there have been applied ever increasing doses and durations of treatment with various antibiotics. Even azithromycin is no exception.

It has been found, and this represents one object of the present invention, that complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals in the form of gels may be used in the obtaining of antiulcer drugs, which has not been as yet described according to the Applicants' Prior Art search.

Complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals are novel and they represent a further object of the present invention.

A further object of the present invention are processes for the obtaining of complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals in high yields as well as of pharmaceutical preparations indicated for the treatment of ulcer diseases.

Particularly there should be cited azithromycin.

As complex- and chelate-forming metals there are used metals of the II and III group, which form physiologically tolerated compounds.

Particularly there should be cited Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} .

The process for obtaining complexes and chelates resp., of azithromycin is performed by means of reacting the antibiotic in the form of free bases or salts, especially hydrochlorides, with salts of bivalent and/or trivalent metals such as Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} , especially chlorides, in a ratio of 2:1, at room temperature, in aqueous solution or in a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, which are used as antacids such as aluminium hydroxide-magnesium carbonate, sucralfate and bismuth subsalicylate, in a ratio of 1:1 to 1:4. The process is most suitably performed with the antibiotic base in alcohol such as methanol or ethanol. The product is isolated in a conventional manner, e.g. by evaporation of the solvent (alcohol) from the reaction mixture under reduced pressure and the isolation of the product by means of filtration.

The product is formulated by known methods into pharmaceuticals such as granules or chewing tablets or aqueous suspensions.

It has been found that the azithromycin chelates with aluminium and magnesium in a ratio of 1:1 to 1:4, in the form of gels as well as with other gels, which are applied as antacids, are retained within 24 hours in the mucous region of the rat stomach in a 1.5- to 60-fold concentrations (Tables 1 and 2), which exceed the Minimal Inhibitory and Bactericidal Concentrations for *Helicobacter pylori* and *Campylobacter jejuni*; accordingly, said preparations are more indicated for the treatment of gastric diseases such as gastric or duodenal ulcers than the parent azithromycin. Furtheron, it has been demonstrated by toxicological investigations that the pharmaceutical formulations do not change the toxicity of the active ingredient.

TABLE I

Concentration of azithromycin in the rat gastric mucosa upon one administration of 60 mg/rat p.o. of
 - azithromycin Al-Mg gel 1:1
 - azithromycin sucralfate gel 1:1
 - azithromycin bi-subsalicylate gel 1:1
 in comparison with azithromycin (30 mg/rat p.o.)

Time h	Azithromycin Al-Mg gel $\mu\text{g/g}$ of tissue	Azithromycin sucralfate $\mu\text{g/g}$ of tissue	Azithromycin bi-subsalicylate $\mu\text{g/g}$ of tissue	Azithromycin $\mu\text{g/g}$ of tissue
5	$\bar{X} = 159.4 \pm 28.66$	$\bar{X} = 100.2 \pm 32.94$	$\bar{X} = 32.5 \pm 8.60$	$\bar{X} = 99.4 \pm 16.61$
18	$\bar{X} = 107.4 \pm 32.04$	$\bar{X} = 75.1 \pm 21.54$	$\bar{X} = 31.3 \pm 10.02$	$\bar{X} = 98.3 \pm 30.71$
24	$\bar{X} = 71.8 \pm 20.41$	$\bar{X} = 74.5 \pm 33.45$	$\bar{X} = 26.1 \pm 5.26$	$\bar{X} = 1.3 \pm 0.08$
32	$\bar{X} = 7.9 \pm 2.88$	$\bar{X} = 36.6 \pm 7.53$	$\bar{X} = 21.1 \pm 3.90$	$\bar{X} = 0$

TABLE 2

Concentration of azithromycin in the rat duodenal mucosa upon one administration of 60 mg/rat p.o. of
 - azithromycin Al-Mg gel 1:1
 - azithromycin sucralfate gel 1:1
 - azithromycin bi-subsalicylate gel 1:1
 in comparison with azithromycin (30 mg/rat p.o.)

Time h	Azithromycin Al-Mg gel $\mu\text{g/g}$ of tissue	Azithromycin sucralfate $\mu\text{g/g}$ of tissue	Azithromycin bi-subsalicylate $\mu\text{g/g}$ of tissue	Azithromycin $\mu\text{g/g}$ of tissue
5	$\bar{X} = 90.0 \pm 14.78$	$\bar{X} = 98.1 \pm 14.17$	$\bar{X} = 73.8 \pm 20.77$	$\bar{X} = 103.5 \pm 7.35$
18	$\bar{X} = 91.3 \pm 13.46$	$\bar{X} = 82.8 \pm 27.11$	$\bar{X} = 62.2 \pm 20.55$	$\bar{X} = 86.1 \pm 33.45$
24	$\bar{X} = 74.3 \pm 29.00$	$\bar{X} = 55.8 \pm 17.04$	$\bar{X} = 40.5 \pm 13.33$	$\bar{X} = 0$
32	$\bar{X} = 7.6 \pm 1.07$	$\bar{X} = 35.6 \pm 18.87$	$\bar{X} = 42.4 \pm 11.25$	$\bar{X} = 0$

The invention is illustrated by the following Examples:

Example. 1

In 50 mL (0.02 mole) of a solution of azithromycin in 95% ethanol there were dissolved 0.067 g AlCl_3 - (0.01 M solution with respect to Al^{+3}) and upon adjusting the pH value to 8.6 with 0.1 N NaOH it was kept stirring for 1 hour at room temperature in a nitrogen stream. Upon addition of 30 mL water the reaction mixture was evaporated under reduced pressure to about half its volume, whereupon it was kept stirring for two hours and the pH was kept constant (pH state) at 8.9 with 0.1 N NaOH. The white precipitate was aspirated, washed with 3 x 10 mL of water and dried, yielding 0.68 g of the product (89.0%), m.p. 125-128° C.

Analysis: Al (atomic absorption spectrometry method):

Calc.: 1.77%

Found: 1.73%

Activity: 852 E/mg *Sarcina lutea* ATCC 9341

Example 2

In accordance with the process described in Example 1 with the sole exception that AlCl_3 was replaced by the addition of 0.136 g $\text{FeCl}_3 \times 6 \text{ H}_2\text{O}$ and the pH was kept at 9.0, there was obtained 0.72 g of a light grey product (92.5%); m.p. 130-133 °C.

Analysis: Fe (atomic absorption spectrometry method):

Calc.: 3.59%

Found: 3.71%

Activity: 840 E/mg *Sarcina lutea* ATCC 9341

Example 3

0.750 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of water under the addition of 1 N HCl (pH approx. 6.0). Subsequently, there were added 0.136 g $\text{FeCl}_3 \times 6 \text{ H}_2\text{O}$ and it was kept stirring upon gradually adjusting the pH value to 8.9 with 0.1 N NaOH. The reaction mixture was kept stirring for 2 hours at a constant pH value, whereupon the light grey product was aspirated, washed with 3 x 10 mL of water, and dried. There was obtained 0.70 g of the product (89.9%). The analysis of the product was identical as in Example 2.

Example 4

In accordance with the process described in Example 1 with the sole exception that AlCl_3 was replaced by the addition of 0.132 g $\text{RhCl}_3 \times 3 \text{ H}_2\text{O}$ there was obtained 0.67 g of a light grey product (83.6%); m.p. 120-123 °C.

Analysis : Rh (polarographic method; 1 M pyridine - 1 M KCl,

$E_{1/2} = -0.40 \text{ V}$; SCE (Saturated Calomel Electrode)

Calc.: 6.42%

Found: 6.15%

Activity: 834 E/mg *Sarcina lutea* ATCC 9341

Example 5

In accordance with the process described in Example 1 with the sole exception that AlCl_3 was replaced by the addition of 0.186 g of $\text{LaCl}_3 \times 7 \text{ H}_2\text{O}$ and the pH was kept at 9.2, there was obtained 0.66 g of a white product (80.5%); m.p. 118-122 °C.

Analysis: La (atomic absorption spectrometry method):

Calc.: 3.47%

Found: 3.10%

Activity: 830 E/mg *Sarcina lutea* ATCC 9341

Example 6

5 In accordance with the process described in Example 1 with the sole exception that AlCl_3 was replaced by the addition of 0.158 g of BiCl_3 , there was obtained 0.70 g of a product (82.0%).

Analysis: Bi (atomic absorption spectrometry method):

10 Calc.: 12.25%
Found: 12.00%

Activity: 812 E/mg *Sarcina lutea* ATCC 9341

15 Example 7

In accordance with the process described in Example 3 with the sole exception that FeCl_3 was replaced by the addition of 0.102 g $\text{MgCl}_2 \times 6 \text{ H}_2\text{O}$ and the pH was kept at 8.6, there was obtained 0.55 g (75.0%) of a white product.

Analysis: Mg (atomic absorption spectrometry method):

25 Calc.: 1.22%
Found: 1.54%

Activity: 850 E/mg *Sarcina lutea* ATCC 9341

30 Example 8

5.0 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of methanol. Upon the addition of 5.0 g of aluminium hydroxide-magnesium carbonate gel it was kept stirring for 2 hours in a nitrogen stream. The suspension was then evaporated to dryness under reduced pressure and the obtained product (9.5 g) was air-dried.

35 Activity: 430 E/mg *Sarcina lutea* ATCC 9341

Example 9

10 In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 10.0 g thereof and that there were used 100 mL of 95% ethanol instead of methanol, there were obtained 14.3 g of the product.

Activity: 295 E/mg *Sarcina lutea* ATCC 9341

45 Example 10

In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 20.0 g thereof, there were obtained 23.5 g of the product.

50 Activity: 160 E/mg *Sarcina lutea* ATCC 9341

Example 11

55 In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of sucralfate, there were obtained 9.5 g of the product.

Activity: 435 E/mg *Sarcina lutea* ATCC 9341

Example 12

In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of bismuth subsalicylate, there were obtained
 5 9.3 g of the product.

Activity: 420 E/mg *Sarcina lutea* ATCC 9341

Claims

- 10 1. The use of complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals in the obtaining of antiulcer drugs.
2. The use as claimed in claim 1, wherein the antibiotic is azithromycin.
3. The use as claimed in claim 1, wherein the metals are chosen from Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} .
- 15 4. The use as claimed in claim 1, of chelates of azithromycin with antacids chosen from the group of salts of Al, Mg, and Bi in the form of gels.
5. The use as claimed in claim 3, of chelates of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.
6. The use as claimed in claim 3, of chelates of azithromycin with sucralfate in the form of gels.
- 20 7. The use as claimed in claim 3, of chelates of azithromycin with bismuth-susalicylate in the form of gels.
8. Complexes and chelates resp., of antibiotics with bivalent and/or trivalent metals.
9. Complexes and chelates resp., as claimed in claim 8, wherein the antibiotic is \bar{z} .
10. Complexes and chelates resp., as claimed in claim 8, wherein the metals are chosen from Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} .
- 25 11. Complexes and chelates resp., of azithromycin with antacids chosen from the group of salts of Al, Mg, and Bi in the form of gels.
12. A chelate of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.
13. A chelate of azithromycin with sucralfate in the form of gels.
14. A chelate of azithromycin with bismuth-susalicylate in the form of gels.
- 30 16. A complex of azithromycin with Mg^{+2} .
17. A complex of azithromycin with Al^{+3} .
18. A complex of azithromycin with Fe^{+3} .
19. A complex of azithromycin with Rh^{+3} .
20. A complex of azithromycin with La^{+3} .
- 35 21. A complex of azithromycin with La^{+3} .
22. Complexes and chelates resp., of azithromycin with Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} in the ratio of 1:1 to 1:4.
23. Complexes and chelates resp., of azithromycin with Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} in the ratio of 2:1.
- 40 24. A process for the preparation of complexes and chelates resp., of antibiotics by means of reacting the antibiotic in the form of free bases or salts, especially hydrochlorides, with salts of bivalent and/or trivalent metals such as Mg^{+2} , Al^{+3} , Fe^{+3} , Rh^{+3} , La^{+3} , and Bi^{+3} , especially chlorides, in a ratio of 2:1, at room temperature, in aqueous solution or in a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, such as aluminium hydroxide-magnesium carbonate, sucralfate and bismuth subsalicylate, in a ratio of 1:1 to 1:4, in an alcohol such as methanol or
 45 ethanol.
25. A process as claimed in claim 24, wherein the antibiotic is azithromycin.

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